Remarks

Claims 52-54 and 56-80 are pending. Claims 54, 64-65, 69, 75 and 80 have been newly canceled. Claims 52, 67, 70, 71-74, 76, 77, 78 and 79 are newly amended. Support for these amendments are found throughout the specification and in the claims as originally filed. No new matter has been entered. The published application US ***20070105121*** is referred to herein as the "Published Application".

Claim Objections

Claim 80 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from a previous multiple dependent claim. See MPEP § 608.01(n). Applicant has cancelled claim 80 thereby rendering its rejection moot.

Claims Rejection - 35 U.S.C. 112, first paragraph- new matter

Claims 64-65, 67, 69, 71-75 and 77-79 are rejected under 35 U.S.C. 112, 1st paragraph, as failing to comply with the written description requirement on the grounds that they comprise new matter.

Specifically, the office action indicates that the recitation of the phrase "blood samples which comprise leukocytes which have not been fractionated into cell types" in claims 71-74 and 77 is new matter. Although Applicant respectfully traverses, solely in the interest of advancing prosecution, Applicant has deleted the phrase from claims 71-74 and 77.

The Office Action indicates that claim 64 contains new matter. When incorporating the limitations of the claims from which it depends, Claim 64 recites:

> "A method for detecting expression of a gene encoding a Charcot-Leyden crystal protein (CLC gene) in a human test subject suspected of having schizophrenia, comprising detecting RNA encoded by said gene in a blood sample of said test subject, using an oligonucleotide of predetermined sequence which is specific for RNA encoded by said gene, and/or for cDNA complementary to RNA encoded by said gene,
> said method further comprises quantifying a level of RNA encoded by said gene in said sample,

> said method further comprising comparing said level of RNA to a quantified level of control RNA encoded by said gene in blood samples of control subjects, wherein said control subjects are classified as healthy subjects,
> said method further comprising classifying said test subject as being a candidate for having schizophrenia if said level of RNA encoded by said gene in said blood sample of said human test subject is higher than that of said control subjects classified as healthy subjects,

the underlined portion being specifically recited in claim 64.

The office action asserts that the:

> "specification does not provide basis for a claim which broadly states that ***any time a test subject's*** RNA expression of "CLC" is ***higher*** than the expression of healthy control subjects that the subject is a candidate for having schizophrenia", emphasis added, paragraph bridging pages 2-3 of the final office action, dated Jan 4, 2008.

Applicant traverses on the grounds that the specification provides support for claim 64, specifically in Working Example 27 and Table 3Y, for example. Working Example 27 demonstrates the use of the claimed invention to detect differential gene expression in blood samples taken from patients with schizophrenia as compared to blood samples taken from healthy patients, and displays the results in Table 3Y. Table 3Y teaches that the ratio of expression in schizophrenic samples relative to control samples is 2.25, indicating that in the tested samples, CLC was expressed, on average at a 2.25 times higher level than in schizophrenic patients versus healthy controls.

Applicant also contends that the recited limitation on the test subject, i.e. a human test subject suspected of having schizophrenia, further limits the claim from the breadth implied by the except above of "***any time a test subject's*** RNA expression of "CLC" is higher than the expression of healthy control subjects that the subject is a candidate for having schizophrenia.

The office action further states:

> "Regarding the expression of CLC, the specification provides only one very specific teaching, while this claim encompasses a broad genus of "higher" expression values".

Applicant traverses this contention of new matter on the grounds that one specific teaching is enough to satisfy the new matter requirement. Applicant traverses this contention of new matter on the grounds that a limitation based on only one specific teaching nevertheless finds sufficient support so as to not constitute new matter. Further, Applicant contends that support for the genus is provided by the specification's teaching that the samples of 4 patients with schizophrenia and six control individuals were tested.

The office action further contends that because Example 51 of the specification, which compares gene expression in patients having schizophrenia vs. patients having manic depression syndrome, is silent with respect to the differential expression of CRC gene, that "this gene is not differentially expressed in schizophrenic patients versus patients with manic depression syndrome". Applicant notes that the claims are drawn to a comparison between a test subject and healthy controls and not controls where the patients have manic depression syndrome. However, in the interest of advancing prosecution, Applicant has cancelled claim 64, without prejudice.

The office action asserts that claims 65, 69 and 75 have new matter. Although Applicant respectfully traverses, solely in the interest of advancing prosecution, Applicant has cancelled claims 65 and 69 without prejudice, rendering their rejection moot.

The office action asserts that claim 67 has new matter by being dependent from claim 65. Accordingly, Applicant has amended claim 67 so it depends from claim 66 as opposed to newly cancelled claim 65. The p value of 0.212 clearly comes under the scope of 0.5.

In light of the above remarks and amendments, Applicant respectfully requests reconsideration and withdrawal of the rejections.

Claims Rejection - 35 U.S.C. 112, first paragraph- enablement

Claims 52-54, 56-74 and 79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that the skilled artisan would have required an undue amount of experimentation to make and/or use

the claimed invention in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art. The enablement rejection will be addressed only to the extent as they apply to the currently pending claims. Applicant has canceled claims 54, 64, 65 and 69, solely in the interest of advancing prosecution, rendering their rejection moot.

Claim 58 is drawn to a method for detecting expression in whole blood of a gene encoding a Charcot Leyden crystal protein (CLC) in a human test subject suspected of having schizophrenia using an oligonucleotide of predetermined sequence specific for CLC. No undue experimentation is required to practice this claim, and there are no problems with unpredictability given the guidance provided by the specification and the data provided in Example 27. Nor are there problems raised with undue experimentation or unpredictability in dependent claims 52, 53, 57, 59 and 60 which contain limitations regarding quantitating the detected expression of a gene encoding a Charcot-Leyden crystal protein (CLC) using techniques well known in the art and disclosed in the specification. Nor are there problems raised with undue experimentation or unpredictability in practicing dependent claims 71 and 72, which contain limitations on the type of blood sample used, since methods to obtain these samples are well known in the art and are described in the specification.

Claim 61 adds the further limitation of comparing the quantified level of RNA encoded by a Charcot-Leyden crystal protein (CLC) gene in a human test subject suspected of having schizophrenia to a quantified level of control RNA encoded by CLC in blood samples of control subjects. Dependent claims 62 and 63 provide further limitations on the types of controls, e.g., healthy subjects, dependent claim 73 contains limitations on the type of blood sample used, and dependent claims 66-68 further require the differential expression of CLC be 2.25 times higher in test versus healthy subjects. Again, no undue experimentation is required to practice claim 61 and those claims dependent from it, and there are no problems with unpredictability given the guidance provided by the specification and the data provided in Example 27.

The methods recited in Claims 58, 52, 53, 57, 59, 60, 61, 62, 63, and 66-68 can be used in methods of classifying expression of a CLC gene in a human test subject, (not classifying a subject). Alternatively, the method of claims 58, 52, 53, 57, 59, 60, 61, 62, 63, and 66-68 can be used in the methods of identifying a gene encoding a Charcot-Leyden crystal protein (CLC gene)

as a candidate biomarker for schizophrenia in a human subject (instant claims 75-76 not subjected to an enablement rejection), thereby satisfying the "how to use" requirement of the statute. Accordingly, Applicant contends that Claims 58, 52, 53, 57, 59, 60, 61, 62, 63, and 66-68 are fully enabled.

The Office action states on page 15 that "claim 58 represents a very narrow embodiment of the claimed invention, but still is based on data that is not replicated" and "that replication is necessary before results can be considered sufficient to support claims directed at classifying the gene expression of an individual test subject". Applicant respectfully disagrees, and submits that the multiple subjects tested per positive and negative control groups in the reduction to practice of claim 58 inherently constitutes a replication, clearly reliably satisfying the language of claim 58, namely: "*detecting expression of a gene encoding a Charcot-Leyden crystal protein (CLC gene) in a human test subject suspected of having schizophrenia, comprising detecting RNA encoded by said gene in a blood sample of said test subject*". Claim 79 is drawn to a method of classifying expression of a gene encoding a Charcot-Leyden crystal protein (CLC gene) in a human test subject, and has been newly amended to particularly point out the claimed invention. The office action states that the specification does not provide sufficient guidance as to how to use the detecting or classification methods", page 15 of the final office action.

Applicant respectfully disagrees. The specification explicitly teaches the use of classification methods in at least paragraphs 0123-0126 and paragraph 0351 of the published instant application. In particular, paragraph 0124 describes methods that can be used for class prediction analysis, and paragraph 0351 describes that blood samples were taken from patients who were diagnosed with schizophrenia as defined herein. Gene expression profiles were then analyzed and compared to profiles from patients unaffected by any disease.".

> Specifically, paragraphs 0123-0125 of the published application state as follows:
>
> [0123] As would be understood to a person skilled in the art, one can utilize sets of genes which have been identified as statistically significant as described above in order to characterize an unknown sample as having said disease or not having said disease. This is commonly termed "class prediction".
>
> [0124] Methods that can be used for class prediction analysis have been

> well described and generally involve a training phase using samples with known classification and a testing phase from which the algorithm generalizes from the training data so as to predict classification of unknown samples (see for Example Slonim, D. (2002), Nature Genetics Supp., Vol.32 502-8, Raychaudhuri et al., (2001) Trends Biotechnol., 19: 189-193; Khan et al. (2001) Nature Med., 7 673-9.; Golub et al. (1999) Science 286: 531-7. Hastie et al., (2000) Genome Biol., 1(2) Research 0003.1-0003.21, all of which are incorporated herein by reference in their entirety).
>
> [0125] As additional samples are obtained, for example during clinical trials, their expression profiles can be determined and correlated with the relevant subject data in the database and likewise be recorded in said database. Algorithms as described above can be used to query additional samples against the existing database to further refine the diagnostic and/or prognostic determination by allowing an even greater association between the disease and gene expression signature.

Thus, classification methods are a well known tool used in the art to refine algorithms to more accurately diagnose disease based on identified biomarkers. Paragraph 0354 of the instant specification further discloses the use of classification of a test sample of an individual to determine whether said individual has schizophrenia or does not have schizophrenia can be done using the differentially expressed genes as shown in Table 3Y, which lists CLC is one. In light of the disclosed use for Claim 79, drawn to a method of classifying expression of a gene encoding a Charcot-Leyden crystal protein (CLC gene) in a human test subject, Applicant contends claim 79 is fully enabled.

The office action states on page 10 that a "method for classifying subjects or for screening subjects as a candidate for schizophrenia which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably make suggestions or drawn conclusions about the presence of schizophrenia, as set forth in the claims" referring to the following assertions:

> "although CLC was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and unpredictable whether it would be expressed in the blood of patients having other mental illnesses or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls", page 10.

The comparison step of claim 79 is between a test subject and both healthy controls and controls with schizophrenia. It does not compare other diseases. The use of the classification method is not disclosed to be an unequivocal diagnosis, but only one method in a battery of diagnostic assays to contribute to a diagnosis of schizophrenia. Further, Claim 79 is not drawn to a method of distinguishing schizophrenia from another mental illness. In contrast, claim 79 is drawn to a classification method, which, as suggested in the office action when read in light of the specification, is designed to be used "to provide a tool that is used as part of a diagnostic process". As such, Claim 79 contain no resolution step of diagnosing schizophrenia, and leaves open the use of other methods to confirm the diagnosis and/or the extent with which CLC is useful as a marker for schizophrenia.

Regarding the concern of the office action that it is unknown and unpredictable whether CLC could be expressed in the blood of patients having another disease, (e.g., RSV, as suggested on page 9 of office action), Applicant notes that even the much litigated patented method claims of Metabolite Laboratories, Inc.'s U.S. Patent No. 4,940,658, ('658), include method steps which can be used to indicate a disease or disorder other than the disease/disorder recited. For example, Claim 13 of '658 is drawn to a method for detecting a deficiency of cobalamin or folate in warm-blooded animals by assaying a body fluid for an elevated level of total homocysteine, and is thus used as a method to detect vitamin deficiency. However, it was well known in the medical community before the filing of '658, that the assay for elevated homocysteine levels could signal an increased risk of heart disease. Despite much scrutiny for other reasons, claim 13 of '658 has not been invalidated as a result of other previously known use(s) of its claimed assay to provide a correlation to a second disease or disorder not recited in its claim 13.

In summary, Applicant believes there is sufficient guidance provided by the specification and that the art is sufficiently predictable such that the amount of experimentation to perform the subject matter within the instant claims is not undue.

In view of the remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection of the instant claims.

Claim Rejections - 35 USC § 103

Claims 52, 53, 54, 57, 58, 60, 61, 62, 63, 71, 72, 73, 75, 76, 77, and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuromitsu et al. (Gene Expression Patterns 1(2001) 17-21) in view of Sharma et al. (WO 98/49342).

Applicant respectfully traverses. Applicant disagrees with the rejection's assertion that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Kuromitsu et al. so as to have additionally tested the blood of the patients having schizophrenia and the healthy control samples using the motivation of Sharma et al. that some diseases may exert a global effect on individuals and that this effect can be measured by gene expression in the blood.

Kuromitsu et al. teach a method for detecting expression of a CLC gene in a human test subject suspected of having schizophrenia comprising detecting RNA encoded by said gene in said subject using an oligonucleotide of predetermined sequence which is specific for RNA encoded by said gene and/or for cDNA complementary to RNA encoded by said gene.

Applicant submits that the generic teaching by Sharma is not sufficient motivation to apply the teachings of Kuromitsu *et al.* to detect expression of a CLC gene in blood of a human test subject having schizophrenia because it provides no substantive scientific basis to predictably arrive at the claimed invention of identifying a CLC gene as a candidate marker for schizophrenia based on its specification.

The Office Action indicates that Sharma et al teaches:

> "From the very early stages of diseases caused by infections, toxic substances, ageing or other conditions changing the quality of life of living eukaryotic organisms, the whole organism responds to the changed condition", page 10, 4th full paragraph, WO 98/49342
>
> and
>
> "The invention is a quick and precise method for the diagnosis of any disease or condition ***that leads to alterations in the activity of genes in a pattern*** which is specific to any particular condition of the organism under observation", emphasis added, page 10, 2nd full paragraph, WO 98/49342.

The latter paragraph indicates that Sharma's teachings do not necessarily apply to every

disease, but only to those disease(s) that "***leads to alterations in the activity of genes in a pattern*** which is specific to any particular condition of the organism under observation. Further, Sharma et al. proffer schizophrenia in a laundry list of potential diseases, including schizophrenia, that their method might apply to, and provides not a single piece of preliminary data of differential expression in whole blood of any RNA with respect to disease.

Accordingly, Applicant contends that the neither the prophetic nor the non-prophetic working examples of Sharma et al. provide sufficient motivation for one of skill reading Sharma's WO document to modify the methods of Kuromitsu et al. by substituting blood for brain tissue as the tissue source to identify markers useful in identifying schizophrenia.

Applicant respectfully traverses, on the grounds that one guideline published by the USPTO for determining obviousness after KSR (Federal Register, Vol. 72, No. 195; October 10, 2007) is that a simple substitution of one known element for another to *obtain predictable results.* As discussed above, Sharma et al.'s prophetic examples do not provide a reliable scientific basis for practicing the claimed methods of identifying biomarkers useful in detecting schizophrenia in blood with a reasonable expectation of success. Thus, it would not have been predictable based on the cited art to one of skill in the art at the time the invention was made, who was considering combining the methods of Kuromitsu et al. with Sharma et al. by substituting blood for the non blood tissue of brain as the substrate upon which to apply the claimed methods to identify CRC as a candidate biomarker for schizophrenia, that such a combined method would be successful and/or predictably arrive at the claimed invention. In the absence of predictability in arriving at the claimed invention by substituting blood for brain tissue in the methods of Kuromitsu et al., one of skill would not have had a reasonable expectation of success in practicing the claimed invention, and thus no prima facie case of obviousness can be made.

Applicant has canceled claims 54 and 75 without prejudice, solely in the interest of advancing prosecution, rendering their rejection moot.

In light of the amendments and above remarks, the Applicant contends that the claims are fully enabled, and respectfully requests reconsideration and withdrawal of the instant rejections.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. No new matter is added. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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